TRANSMITTAL OF APPEAL BRIEF

Docket No. MXI-170

In re Application of: Jan G.J. VAN DE WINKEL

Application No.	Filing Date	Examiner	Group Art Unit
09/820099-Conf. #2545	March 27, 2001	L. R. Helms	1642

Invention: METHODS FOR IMMUNOSTIMULATION USING BINDING AGENTS FOR THE FC RECEPTOR OF IMMUNOGLOBULIN A

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed: March 16, 2004 .

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Dated: July 16, 2004

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Dated: July 16, 2004 Signature: _____ (Jeanne M. DiGiorgio)

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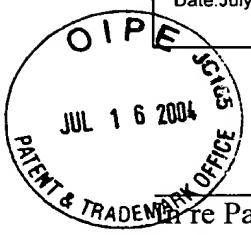
Date: July 16, 2004 Signature: _____ (Jeanne M. DiGiorgio)



Docket No.: MXI-170
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jan G.J. van de Winkel

Application No.: 09/820099 Art Unit: 1642

Filed: March 27, 2001 Examiner: L.R. Helms

For: METHODS FOR IMMUNOSTIMULATION USING BINDING AGENTS FOR THE FC RECEPTOR OF IMMUNOGLOBULIN A

APPEAL BRIEF

MS Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

As set forth in the Notice of Appeal received by the Patent Office on March 16, 2004, Appellant hereby appeals the final decision of the Examiner dated November 20, 2003 rejecting claims 1 and 6-12 of the above-identified application.

A request for the appropriate extension of time and fee are being submitted herewith. The fee for the Appeal Brief Fee as set forth in 37 C.F.R. §1.17(f) is also being submitted herewith. No other fees are believed to be due in connection with the filing of this Appeal Brief.

Appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of claims 1 and 6-12.

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I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Medarex, Inc., the assignee of the entire right, title and interest in the application as recorded with the Patent Office on July 16, 2001 at Reel 011989, Frame 0065.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellant, or Appellant's legal representative, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1 and 6-12 are pending. All other claims, claims 2-5 and 13-24, have been canceled. Claims 1 and 6-12 have been finally rejected and are currently on appeal. An Appendix of the claims on appeal is included with this Appeal Brief.

IV. STATUS OF THE AMENDMENTS

No amendments after final have been submitted. All other amendments have been entered.

V. SUMMARY OF THE INVENTION

Appellant's invention, as encompassed by the claims on appeal in the present application, pertains to a method for eliminating a target cell or antigen from the circulatory system of a subject by administering a complex comprising monomeric IgA, or a portion thereof, that binds to FcαRI and which is linked to a second portion that specifically binds the target cell or antigen (as described in Appellant's disclosure, for example, at page 2, lines 27-3).

In a preferred embodiment, the second portion of the complex comprises an antibody or an antibody fragment thereof which specifically binds the target cell or antigen, *e.g.*, a cancer cell, a bacteria, a virus, or a fungus (as described in Appellant's disclosure, for example, at page 3, lines 7-9).

Appellant's method for eliminating a target cell or antigen from the circulatory system of a subject can further include the step of administering to the subject a cytokine, *e.g.*, GM-CSF,

IL-6, IL-1β, IL-8, and TNF-α, which increases expression of FcαRI on Kupffer cells (as described in Appellant's disclosure, for example, at page 3, lines 18-22).

In another embodiment, the complex is administered by injection, *e.g.*, intravenously (as described in Appellant's disclosure, for example, original claim 12).

VI. STATEMENT OF ISSUES PRESENTED FOR REVIEW

Appellant presents the following issue for review: whether claims 1 and 6-12 are patentable under 35 U.S.C. §103(a) over Shen *et al.* (WO 98/23646) as evidenced by Monteiro *et al.* and Appellant's own specification.

VII. GROUPING OF CLAIMS

Claims 1 and 6-12 are Appellant's principal claims on appeal. Claim 1, the sole independent claim, is drawn to a method for eliminating a target cell or antigen from the circulatory system of a subject comprising, administering to the subject a complex comprising monomeric IgA, or a portion thereof that binds to FcαRI, linked to a second portion which specifically binds the target cell or antigen.

Claims 6-9 and 11 depend from the above described independent claim 1.

Claim 6 is directed to the method of claim 1 wherein the second portion of the complex comprises an antibody, or an antibody fragment thereof, which specifically binds the target cell or antigen.

Claim 7 is directed to the method of claim 1 wherein the target cell is a cancer cell.

Claim 8 is directed to the method of claim 1 wherein the target antigen is selected from the group consisting of a bacteria, a virus, and a fungus.

Claim 9 is directed to the method of claim 1 further comprising the step of administering to the subject a cytokine which increases expression of FcαRI on Kupffer cells.

Claim 11 is directed to the method of claim 1 wherein the complex is administered by injection.

Claim 10 depends from claim 9 and is directed to the cytokine being selected from the group consisting of GM-CSF, IL-6, IL-1β, IL-8, and TNF-α.

Claim 12 depends from claim 11 and is directed to the complex being administered intravenously.

VIII. ARGUMENTS

A. Rejection of Claims 1 and 6-12 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Shen *et al.* (WO 98/23646) as evidenced by Monteiro *et al.* and the Present Specification

The Examiner has finally rejected claims 1 and 6-12 under 35 U.S.C. §103(a) "as being unpatentable over Shen *et al.* (WO 98/23646) as evidenced by Monteiro *et al.* and the specification."

Specifically, the Examiner states that:

> Shen *et al.* teach binding agents specific for the FcαR and [that] the binding agents trigger an Fc mediated effector cell activity such as phagocytosis (see page 1). Shen *et al.* also teach bifunctional binding agents comprising an agent that binds FcαRI and a bacteria (see page 22) or cancer cell or antigen (see page 19-20) thereof, further is a method for eliminating cells or antigen in a subject by administration of the bispecific agent to a subject (see page 28-29) . . . and the binding agents bind the FcαR with the same affinity as a type of IgA which can be monomeric IgA (see page 6). As evidenced by Monteiro *et al.* (and the specification at page 1, lines 6-8) there is only a single class of IgA Fc receptor, FcαRI, therefore since the agent binds to FcαRI, it would be obvious that the agent would bind to FcαRI expressed on Kupffer cells . . .

The Examiner acknowledges that "Shen *et al.* does not specifically teach that the binding agent can be monomeric IgA." However, the Examiner asserts nonetheless that "it would have been obvious to have the binding agent be monomeric IgA linked to a second antibody because monomeric IgA would bind with the same affinity as a type of IgA and it would bind to the IgA site and perform phagocytosis." Based on this, the Examiner concludes that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have used a complex comprising monomeric IgA linked to a second antibody (a bispecific agent) for the elimination of a target cell or antigen."

The Examiner's rejection is based on the erroneous assumption that it would have been obvious to have substituted monomeric IgA as the binding agent for FcαR in the bispecific molecule taught by Shen *et al.* In contrast to the binding agents for FcαR (*e.g.*, antibodies directed against FcαR) taught by Shen *et al.*, monomeric IgA naturally functions as a bispecific molecule that binds both to FcαR and a target antigen. As discussed by Shen *et al.*, monomeric IgA binds to FcαR via its constant region and to a target antigen via its variable region. Thus,

unlike the agents that bind FcαR taught by Shen *et al.*, such as IgG antibodies and antibody fragments (*e.g.*, Fab' fragments) directed against FcαR, there would have been no motivation to have linked monomeric IgA to a second binding specificity for a target antigen to direct effector cells expressing FcαR to the target antigen.

Indeed, the bispecific molecules taught by Shen *et al.* involve the linking of two separate binding agents, one for FcαR and one for a target antigen, for the purposes of directing FcαR expressing effector cells to the target antigens. Shen *et al.* do not teach or suggest the use of monomeric IgA, nor would it have been obvious to have used monomeric IgA, since this molecule was already known to have such dual binding specificity and, importantly, because Shen *et al.* teach several advantages of not using monomeric IgA. Specifically, targeting antigens is made more effective by using a binding agent that does not compete with natural ligand for binding to FcαR (*e.g.*, by using an antibody that binds to FcαR at a site distinct from the natural ligand (*i.e.*, IgA) binding site). Thus, Shen *et al.*, in fact, teach away from using the natural ligand (*e.g.*, monomeric IgA) in the bispecific molecules of their invention.

Moreover, Appellants respectfully note that there are two forms of natural ligand for FcαR, monomeric and dimeric IgA. At the time of the present invention, the role of monomeric IgA was poorly understood. While it was known that monomeric IgA binds to FcαR and activated certain effector cell functions, the role of the molecule *in vivo* was poorly understood. In contrast, the role of dimeric IgA (which was also known to bind to IgA) as a "first line of defense" in preventing adherence of bacteria to mucosal surfaces was already understood. Thus, even if one of ordinary skill in the art had been motivated to have substituted natural ligand for FcαR in place of the binding agents for FcαR taught by Shen *et al.*, one of ordinary skill in the art would have been motivated to have used dimeric IgA, not monomeric IgA, as a binding agent for FcαR in light of the better understood role of dimeric IgA in eliminating pathogens.

For at least the foregoing reasons, the method of claims 1 and 6-12 is patentable in view of Shen *et al.*

IV. CONCLUSION

Appellant submits that claims 1 and 6-12 are patentable and it is respectfully requested that the Board reverse the final rejection of claims 1 and 6-12 for the reasons given above.

Respectfully submitted,

Dated: 16 July 04

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APPENDIX OF CLAIMS ON APPEAL

1. (Previously Presented) A method for eliminating a target cell or antigen from the circulatory system of a subject comprising, administering to the subject a complex comprising monomeric IgA or a portion thereof that binds to FcαRI, linked to a second portion which specifically binds the target cell or antigen.

2-5. (Canceled)

6. (Original) The method of claim 1, wherein the second portion of the complex comprises an antibody or an antibody fragment thereof which specifically binds the target cell or antigen.

7. (Original) The method of claim 1, wherein the target cell is a cancer cell.

8. (Original) The method of claim 1, wherein the target antigen is selected from the group consisting of a bacteria, a virus, and a fungus.

9. (Original) The method of claim 1, further comprising the step of administering to the subject a cytokine which increases expression of FcαRI on Kupffer cells.

10. (Original) The method of claim 9, wherein the cytokine is selected from the group consisting of GM-CSF, IL-6, IL-1β, IL-8, and TNF-α.

11. (Original) The method of claim 1, wherein the complex is administered by injection.

12. (Original) The method of claim 11, wherein the complex is administered intravenously.

13. - 24. (Canceled)